

# A dynamic Bayesian Markov model for health economic evaluations of interventions against infectious diseases

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## Abstract

Health economic evaluations of interventions against infectious diseases are commonly based on the predictions of compartmental models such as ordinary differential equation (ODE) systems and Markov models. In contrast to standard Markov models which are static, ODE systems are dynamic by definition and therefore able to account for the effects of herd immunity. This is crucial in pathogens which are transmissible between humans to prevent incorrect model outcomes. The computational effort of fully probabilistic ODE systems is considerably high. Thus, most ODE-based models in the literature are deterministic; they do not account for parameter uncertainty and probabilistic sensitivity analysis cannot be conducted straightforwardly. Yet, it is an essential part of health economic evaluations to investigate the impact of parameter uncertainty on decision making. We present an innovative approach of a dynamic Markov model with Bayesian inference. We extend a static Markov model by directly incorporating the force of infection of the pathogen into the health state allocation algorithm, accounting for the effects of herd immunity. As a consequence, the output of our fully probabilistic Bayesian Markov model is based on dynamic interactions between individuals, and at the same time eligible to conduct probabilistic sensitivity analysis straightforwardly. We introduce a case study of a fictional chronic sexually transmitted infection. By means of this constructed example, we show that our methodology produces results which are comparable to a Bayesian ODE system, yet at lower cost of implementation and computation. In contrast to probabilistic methodology, deterministic models tend to underestimate disease prevalence and thus the benefits of vaccination.

## 1 Introduction

Vaccines against infectious diseases offer major health benefits to society [1, 2] and have been instrumental in the prevention of conditions previously causing egregious burden from the public health perspective. Examples include the worldwide eradication of smallpox [3] and the extremely low incidence of tetanus, diphtheria, congenital rubella syndrome, mumps and measles in the Western world [4]. However, despite being frequently successful from a clinical point of view, vaccination programmes are often costly and complex to apply to the target population. Given that publicly funded health care systems such as the UK National Health Service face increasing budget limitations, health interventions (including vaccination programmes) are increasingly subject to cost-effectiveness analyses (CEAs) [5, 6] as a pre-requisite to their implementation.

The National Institute for Health and Care Excellence (NICE) is arguably the leading health technology assessment agency in the world. In the UK, NICE is responsible for providing guidance and advice on whether proposed interventions should be publicly funded. Over the years, NICE has developed a set of criteria and guidelines that drive the analytic process of CEA [7]. Crucially, these involve the explicit necessity of assessing the impact of structural and parameter uncertainty on the decision making outcome, a process typically known as *Probabilistic Sensitivity Analysis* (PSA) [6, 8, 9].

Interestingly, in the UK the assessment and appraisal of vaccines falls under the remit of the Joint Committee for Vaccines and Immunisations, an independent expert advisory committee

to the ministers and health departments. Since 2009, the Health Protection Regulation obliges the Secretary of State to ensure that recommendations for national vaccination programmes are based on an assessment demonstrating cost-effectiveness [10]. However, there are currently no vaccine-specific guidelines for developing clinical or cost-effectiveness evidence.

One of the reasons for this circumstance is perhaps the intrinsic complexity of infectious disease modelling, which is typically performed through *compartmental* models. These are highly complicated mathematical tools capable of simulating the natural history of disease infection and progression. More specifically, in pathogens transmissible among humans, these models need to account for population dynamics and the effects of *herd immunity* [11]. Due to lower infection prevalence, the introduction of a preventive measure such as vaccination induces a reduced risk of pathogen exposure. Only dynamic models are able to prevent incorrect predictions since they are suitable to incorporate these effects [12, 13].

From the technical point of view, dynamic compartmental models are usually fitted by solving systems of Ordinary Differential Equations (ODEs). While these automatically deal with features such as herd immunity (and thus are considered the “industry standard” in infectious disease modelling), they are almost invariably characterised by a notable computational effort. One important consequence is that, in most cases, epidemiological and economic modelling for infectious disease performed by means of ODEs is based on a deterministic framework. This is relevant because in order to perform a full PSA, it is necessary to quantify the joint uncertainty in the model parameters through a probabilistic model output. In the context of ODE models, sampling methods such as the Latin Hypercube Sampling [14] can be used to add stochasticity, as shown in [15–17]. However, they are rather complex and computationally intensive. In addition, they are prone to result in a biased outcome on the natural history of disease since parameter uncertainty is not accounted for directly in the compartmental model, but only in retrospect.

The difficulties in producing a probabilistic output of ODE systems might be one of the reasons why the *International Society for Pharmacoeconomics and Outcomes Research* guideline for best modelling practice in infectious disease suggests that PSA is *not* a fundamental component of health economic assessment [12]. This recommendation is given in contrast with NICE and virtually any other disease area. As a consequence, most economic models for vaccines only consider deterministic sensitivity analysis, which is based on selecting a grid of “plausible” values for a subset of model parameters in order to assess the robustness of the decision-making process. This approach is however not recommended in general, as it fails to account for potential correlation among the parameters [6, 9, 18].

An alternative compartmental specification is given by multi-state models — in the health economics literature these are often referred to as Markov models (MMs). MMs are used to model progression over time across a finite set of health states. Although MMs can also be computationally intensive, it is generally feasible to make them fully probabilistic (e.g. using a Bayesian framework) or to use re-sampling methods such as the bootstrap to characterise the uncertainty in the model parameters. Perhaps for this reason, MMs are a very popular tool in health economic evaluation. Nevertheless, a major limitation in infectious disease modelling is that they are intrinsically static, i.e. they do not account for population dynamics [19].

With a view to simplifying the process of PSA in health economic models of interventions for infectious diseases, we introduce in this paper an extension to standard MMs, which we term dynamic Bayesian MMs. We directly include the force of infection of the pathogen, which automatically accounts for dynamic interactions between individuals and therefore the effects of herd immunity, into the state allocation algorithm of a standard MM. In other words, the movement of a susceptible individual to the state of infection is directly represented by the dynamic force of infection. Our approach does not involve ODEs. The Bayesian framework with its probabilistic nature is highly flexible since it considers multiple sources of prior information in terms of evidence synthesis [20]. In addition, as an essential part of CEAs, PSA can be conducted in a straightforward manner.

The paper is structured as follows: Firstly, we describe compartmental models in widespread use for CEAs on interventions against infectious diseases. Secondly, we introduce our innovative approach. Thirdly, we compare the performance of a deterministic and a probabilistic ODE-based model to our methodology, using a case study of a chronic sexually transmitted infection. To contrast the three methodologies in practice, we evaluate different scenarios with varying levels of parameter uncertainty, calculate the infection prevalence, and conduct CEAs including PSA, comparing a screening strategy to a hypothetical vaccine. Finally, we discuss advantages and disadvantages of ODE-based methodology in comparison to the dynamic Bayesian MM.

## 2 Compartmental models for infectious diseases

Compartmental models consist of a set  $\mathcal{S}$  of mutually exclusive and exhaustive states describing disease infection and progression. We indicate the elements of  $\mathcal{S}$  as  $s = 1, \dots, S$ . Individuals move across the states over a pre-specified time horizon. Figure 1 shows an example of a compartmental model incorporating the natural disease history of a chronic sexually transmitted infection (STI) with  $S = 5$  states. The assumptions encoded by this structure are that individuals are initially in the state *Susceptible* (indexed by  $s = 1$ ), from which they can move to the state *Infected* ( $s = 2$ ). Following this, a proportion of individuals move to an *Asymptomatic* state ( $s = 3$ ). Those who progress further to the state *Morbid* ( $s = 4$ ) develop disease symptoms. The state *Dead* ( $s = 5$ ) can be reached from any state; individuals die due to any cause or as a consequence of being in the state *Morbid*. Compared to the average population, the latter have a higher risk of death. A transition from one state to another is defined according to suitable *transition parameters* [21]. They are indicated as  $\phi_{r,s}$ , where  $r, s \in \mathcal{S}$  represent the original and target state, respectively. We consider an open model structure in which living individuals are able to proliferate at a rate  $\chi$ , resulting in a replenishment of the pool of individuals at risk of contracting the infection.

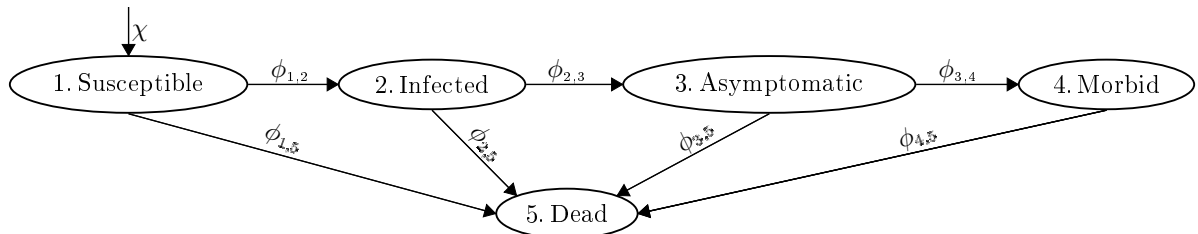


Figure 1: Model structure of a hypothetical chronic sexually transmitted infection consisting of five states. The arrows represent the possible transitions. These are governed by the parameters  $\phi_{r,s}$  with indices  $r, s \in \mathcal{S}$  representing origin and target states, respectively. The replenishment of the pool of susceptibles by newborn individuals proceeds at a rate  $\chi$ .

Compartmental models may differ in three important characteristics. The first is the specification of time. The most realistic option is to allow transitions among the states to happen at any point in time  $t > 0$ ; this is a so-called “continuous-time approach”. Alternatively, it is possible to assume that transitions occur in discrete time where only one transition is possible within a pre-defined time interval  $\mathcal{I}_t = [t, t + \kappa)$ , where  $\kappa$  determines the corresponding interval width, commonly referred to as *cycle*. Depending on the medical context,  $\kappa$  can be specified in terms of daily, weekly, monthly or yearly cycles. The second difference concerns the way in which interactions among individuals are considered: models which account for dynamic interactions between individuals in a population are referred to as *dynamic*, while those that do not and thus ignore the effects of herd immunity are termed *static*. The third difference, which has major impact in the context of health economic evaluation, is related to the way in which a compartmental model deals with parameter uncertainty. Deterministic models use a relevant summary,

for example obtained from some available data as a plug-in point estimate for the corresponding model parameter. In contrast, in probabilistic models the parameters are associated with probability distributions and their uncertainty is propagated through the infection progression. While frequentist versions of this strategy exist (e.g. based on bootstrap), this type of modelling is most naturally handled within a Bayesian paradigm.

## 2.1 Ordinary Differential Equation models

ODE systems model the rate of change in the number of individuals within a given state over continuous time. The parameters are thus transition *rates* and we denote them as  $\rho_{r,s}(t)$ , with  $r, s \in \mathcal{S}$  representing again the origin and target states, respectively. In principle, transition rates can depend on  $t$ , but do not necessarily have to. The number of individuals transitioning in each state at  $t$  is multiplied by the corresponding transition rates to obtain the inflow and outflow to and from a state. The difference between the number of individuals entering and leaving a state corresponds to the derivative of the number of individuals in the respective state.

Back to our example, we define the vector  $\mathbf{n}(t) = (n_1(t), \dots, n_S(t))'$ , where  $n_s(t)$  is the number of individuals in state  $s$  at time  $t$ . The corresponding ODE system is given by the set of equations

$$\begin{aligned}\frac{dn_1(t)}{dt} &= \chi[n_1(t) + n_2(t) + n_3(t) + n_4(t)] - \rho_{1,2}(t)n_1(t) - \rho_{1,5}n_1(t) \\ \frac{dn_2(t)}{dt} &= \rho_{1,2}(t)n_1(t) - \rho_{2,3}n_2(t) - \rho_{2,5}n_2(t) \\ \frac{dn_3(t)}{dt} &= \rho_{2,3}n_2(t) - \rho_{3,4}n_3(t) - \rho_{3,5}n_3(t) \\ \frac{dn_4(t)}{dt} &= \rho_{3,4}n_3(t) - \rho_{4,5}n_4(t) \\ \frac{dn_5(t)}{dt} &= \rho_{1,5}n_1(t) + \rho_{2,5}n_2(t) + \rho_{3,5}n_3(t) + \rho_{4,5}n_4(t).\end{aligned}\tag{1}$$

To estimate transition rates, retrospective or prospective event history data are commonly used [21]. Retrospective records are defined as the time to a certain event after a pre-specified starting point. In contrast, survival data are prospective; individuals under risk are observed over a follow-up period until death or censoring occurs. The corresponding transition rates are estimated by means of differentiation. For example, the derivative of the cumulative distribution function of the probability of survival until a certain time point  $t$  is the rate of death at  $t$ .

The rate of change in the number of individuals in each state at each point in time  $t$  is subject to population dynamics, interactions among individuals and exposure to sources of infection. The transition to the state of infection is determined by the dynamic, time-specific force of infection of the pathogen, indicated by  $\rho_{1,2}(t)$  in (1). This is a function of the probability of pathogen transmission, contact patterns between individuals and population prevalence.

In a deterministic analysis of an ODE system, a point estimate (e.g. mean, median or mode) is usually taken from available data to inform the model parameters. For example, the transition rate to the state of infection corresponds to a summary statistic of the infection incidence. Thus, the model parameters do not vary due to the influence of stochastic effects; this unrealistic assumption is likely to result in a biased model outcome. Scenario analyses are often also performed, for example by plugging in more extreme estimates (e.g. lower or upper quantiles) for the parameters. As mentioned earlier, this is not equivalent to the application of a full PSA.

Theoretically, it is possible to conceive of a fully probabilistic version of an ODE-based model; for example, in a Bayesian context, uncertainty in the relevant parameters that determine the transition rates can be considered by means of probability distributions. The uncertainty is then propagated through the estimation procedure, which again generates a full distribution of outcomes. This type of model can be analysed using for instance Markov Chain Monte Carlo

(MCMC) samplers such as **BUGS** [22] (via the interface **WBDiff**) or **Stan** [23], a very promising tool, which in general performs extremely well with relatively complex systems. Both include ODE solvers and can be linked to the statistical programming language R.

However, **WBDiff** is generally computationally intensive and the ODE solvers provided by **Stan** may struggle in “stiff” regions of ODE systems, where the underlying numerical solver becomes unstable unless the step-size is set to very small values (although we acknowledge some very recent developments aimed at improving the performance of the sampler in such cases). More importantly, in realistic problems including a large number of states and complex structures, fully probabilistic ODE models may be impractical since the model needs to be run for a large number of simulations to ensure convergence of each parameter and thus the ODE system has to be solved repeatedly for each parameter combination. The increase in the computational time is mainly induced by the length of the observation time horizon, the amount of probabilistic model parameters, the complexity of interactions between individuals, the number of differential equations in the ODE system and their nature (stiff, non-stiff, or a combination of both). Consequently, complex ODE-based models which are fully probabilistic are rare exceptions in the literature on infectious disease transmission modelling [24].

## 2.2 Discrete-time Markov models

The main characteristic of MMs is that movements of individuals between states are subject to a Markov assumption. Typically it is assumed that the chance of moving to a future state depends only on the current state, but not on the full trajectory. Similarly to ODE-based models, MMs can be implemented for continuous time; in this case, the two approaches differ in the way they describe the process of transitions. As suggested earlier, in the former, the rates of change are calculated dynamically through differentiation, while in the latter, the transitions are described by a static and “memoryless” Markov process.

However, the vast majority of MMs in the health economic literature is based on a discrete-time approach [25]. In this case, individuals move across the states according to a set of transition *probabilities* only once per time interval (commonly referred to as “Markov cycle” ). These probabilities can be arranged in a matrix  $\mathbf{\Pi} = (\pi_{r,s})$ , whose elements represent the transition probabilities for movements from an original state  $r$  to a target state  $s$ .

For the model structure of Figure 1, the transition probability matrix is defined as

$$\mathbf{\Pi} = \begin{pmatrix} \pi_{1,1} & \pi_{1,2} & 0 & 0 & \pi_{1,5} \\ 0 & \pi_{2,2} & \pi_{2,3} & 0 & \pi_{2,5} \\ 0 & 0 & \pi_{3,3} & \pi_{3,4} & \pi_{3,5} \\ 0 & 0 & 0 & \pi_{4,4} & \pi_{4,5} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}, \quad (2)$$

implying that, for example, a susceptible individual either acquires the infection (with probability  $\pi_{1,2}$ ), dies (with probability  $\pi_{1,5}$ ), or remains susceptible, which occurs with probability  $\pi_{1,1} = 1 - \pi_{1,2} - \pi_{1,5}$ .

If we define the vector  $\mathbf{n}_t = (n_{1t}, \dots, n_{5t})'$ , where  $n_{st}$  is the number of individuals in state  $s$  and at each time interval  $\mathcal{I}_t$ , then transitions of individuals across the states from one time interval to the next are calculated as

$$\mathbf{n}_{t+1} = \mathbf{\Pi} \mathbf{n}_t. \quad (3)$$

The transition probabilities can be estimated by individual-level or aggregate data. Individual-level data, e.g. collected through clinical trials or observational studies, contain specific information on every single individual during the follow-up. In contrast, aggregate data summarize the disease outcome over the whole study population, commonly stratifying for relevant covariates such as age, sex or comorbidities.

MMs are relatively straightforward to implement and are commonly used to model the progression of non-communicable conditions such as cardiovascular disease and cancer. Therefore, they are established in the health economic literature and well-known to both clinicians and decision makers. Crucially, however, the process of pathogen transmission is not estimated correctly by standard MMs. In fact, because of the Markov property, a movement to a future state does not account for dynamic interactions between individuals. A transition of susceptibles to the state of infection is represented by a static transition parameter which does not consider changes in the population prevalence over time. These especially occur after the introduction of a preventive intervention such as vaccination into a fully susceptible population, induced by the effects of herd immunity. Since standard MMs are not able to account for herd immunity, their population prevalence predictions are commonly biased (although notable exceptions include scenarios with very low vaccine coverage or pathogens that cannot be transmitted between individuals, e.g. tetanus). In the worst case, the whole model outcome on infection prevalence and the related CEA can be incorrect, e.g. because of the impact of an unrecognised shift in the age of infection of childhood diseases. Some childhood diseases are relatively harmless in young children but prone to lead to serious health issues in adults. The consequences of biased predictions of static MMs on population health and induced costs, e.g. through hospitalisation and treatment, can have dire consequences [19].

### 2.3 Hybrid models

An interface between static and dynamic alternatives is given by the so-called *hybrid* models. These are combinations of the two different versions of models. First a dynamic transmission model, commonly based on ODEs, is implemented to estimate infection prevalence. Then the prevalence estimate is used as input for the natural history model of disease progression, which is for example a static MM or microsimulation model. As a consequence, the disease acquisition depends on contact patterns between individuals. Examples in the health economics literature include [26, 27].

While useful in some circumstances, a hybrid approach has several drawbacks. First, the transmission models involved are commonly deterministic. Consequently, even if PSA is performed on the disease progression part of the hybrid model, it does not refer to the crucial disease transmission component. Second, hybrid models are extremely complex since they consist of two separate components based on different methodologies. These are run sequentially since an interim step is necessary to include the estimated prevalence results into the disease progression model.

## 3 Dynamic Bayesian Markov models

To overcome the limitations discussed above and with a view to extending the modelling framework for health economic evaluation of interventions in infectious disease, the main idea behind our proposed model is to add dynamic interactions between individuals into a standard MM setting. We do so by including the force of infection into the definition of the transition probabilities from the state *Susceptible* to the state *Infected*. Specifically, we set up our model so that the force of infection is calculated separately within each cycle of the state allocation algorithm corresponding to (3) as a function of

- the probability of pathogen transmission per contact, which we indicate as  $\beta$ ;
- the active contact rate,  $\omega$ ; and
- the time-dependent pathogen prevalence

$$\psi_t = \frac{I_t}{N_t},$$

where  $I_t$  represents the number of infectious individuals and, assuming that state  $S$  indicates death,

$$N_t = \sum_{s=1}^{S-1} n_{st}$$

is the total number of individuals alive at time interval  $\mathcal{I}_t$ .

The force of infection is recalculated at each Markov cycle as

$$\lambda_t = \beta\omega\psi_t. \quad (4)$$

Since  $\omega$  is a rate, (4) also results in a transition rate. Assuming that  $\lambda_t$  remains constant within each time interval, the corresponding time-dependent transition probability for the discrete-time MM can be estimated as

$$\pi_{1,2,t} = 1 - \exp^{-\lambda_t}. \quad (5)$$

The assumption of uniformity within the intervals  $\mathcal{I}_t$  is not likely to hold if the disease is characterised by very fast transmission, or when events associated with the infection are likely to occur in short periods of time. In these cases, it is perhaps advisable to reduce the length of the cycles  $\kappa$  and the duration of the follow up for the “virtual” cohort.

This probability can be multiplied by the number of individuals in the state *Susceptible* to provide an estimation of the contingent of individuals who move to the state *Infected*, effectively including dynamic, time-dependent changes in the population prevalence in the corresponding transitions.

In comparison to more complex hybrid models, our approach does not require two separate modules for disease transmission and progression. In addition, computational time is reduced by fitting models that do not involve complex ODEs, while still allowing for mixing patterns within the population. A third potential advantage of the dynamic MM framework is that it is fairly simple to make the model fully probabilistic. This is particularly relevant because, for obvious ethical and practical reasons, it is invariably difficult (if possible at all) to obtain and use experimental evidence to inform the pathogen transmission probability  $\beta$  and the active contact rate  $\omega$  — arguably the crucial parameters. Often observational studies or expert opinions are the only available information with the consequence that large uncertainty remains over the most likely range, let alone the “true” value of the parameters. A Bayesian approach may provide great benefit in allowing this uncertainty to be fully propagated and perhaps in integrating different sources of evidence (e.g. using evidence synthesis [21]); this indeed has been advocated for MMs in the health economics literature [9, 21, 28].

In a Bayesian dynamic MM setting, it is possible to assign prior distributions to the parameters  $(\beta, \omega)$  to represent the state of science — if data are available, these are updated into posterior distributions although it is possible to still propagate uncertainty in the priors even when no data on pathogen transmission or active contacts are observed. In addition, the quantity  $\psi_t$  is estimated for each cycle as a function of transition probabilities, which can also be modelled using suitable distributions. This modelling process induces a probability distribution on  $\psi_t$  and a fortiori also on  $\lambda_t$ , which is defined as a function of the three random parameters  $(\beta, \omega, \psi_t)$ . Thus, the corresponding transition probabilities  $\pi_{1,2,t}$  are modelled probabilistically, meaning that uncertainty in the population dynamics is propagated through the economic model.

As suggested earlier, another crucial aspect in infectious disease modelling (and more generally in statistical analysis) is that of calibration of the model output [29, 30]. In a Bayesian framework, the transition probabilities can be calibrated directly in the process of updating the prior into the corresponding posterior distributions. For example, available data on the number of individuals progressing to a more severe state following infection as observed in large population registries can be used to update the prior distribution of the corresponding transition

probability (although, technically, care is needed to account for the fact that, usually, available data commonly refer to the whole population under risk, while a transition probability from one state to another only refers to the number of individuals in the original state).

Finally and specifically for the purpose of economic evaluation, the dynamic BMM has the advantage that PSA can be performed “for free”, once the model output is produced. In a Bayesian framework, the MCMC simulations for all the model parameters can be combined to obtain a full characterisation of the uncertainty in the decision-making process. This can be post-processed (e.g. using the R package **BCEA** [31]) to produce relevant summaries such as the cost-effectiveness plane, the cost-effectiveness acceptability curve (CEAC) and the analysis of the value of information (we describe these in details in the next session).

## 4 Case study

We consider again the fictional chronic STI described above and compare our methodology of a dynamic Bayesian MM to both a deterministic and a probabilistic ODE-based model, based on a full Bayesian approach. In the following, we denote the three models as BMM, dODE and BODE, respectively. We investigate the shortcomings of the deterministic model and evaluate whether our BMM produces results that are in line with the BODE. Notice that we consider the BODE as the gold standard, for the purposes of a full cost-effectiveness analysis.

In the three approaches compared, we distinguish between sexes as well as high- and low-risk sexual behaviour. The duration of the follow up is set at 100 years. We consider a population of 1,000,000 individuals and initially assume that 99.94% of these are susceptible, whereas the remainder are infected. Males amount to 50% and the high-risk group to 20% of the population; the sex ratio in the two risk groups is equivalent. The proportion of infected individuals in both sexes and risk groups is identical. We account for sex-specific differences in sexual behaviour, assuming higher partner acquisition rates in males. The population size changes due to births and deaths. We conduct our analysis for two competing health-care interventions. In the *status-quo*, individuals are screened in intervals of five years at a pre-defined rate to enable an early detection of the STI. Under the *vaccination* scenario, no screening takes place; instead, susceptible individuals are vaccinated in the same time frame at a specified vaccine uptake rate. Following STI diagnosis, treatment is provided in both interventions.

All rates of change in the ODE systems differ according to the two characteristics considered; we refer to these using the indices  $v, v' = (Male, Female)$  to indicate an individual’s sex and its opposite and  $b = (Low, High)$  to indicate the individual’s sexual behaviour group. In the ODE model, only the transition rate  $\rho_{v,b,1,2}(t)$  from the state *Susceptible* to the state *Infected* depends on the covariates sex and behaviour, whereas in the BMM the estimation of the transition probability  $\pi_{v,b,1,2,t}$  affects the transition probability  $\pi_{1,1}$  of remaining in the state *Susceptible*. This is a consequence of the definition of transition probabilities for movements from a certain state which must sum up to 1.

We assume a yearly Markov cycle length. To reduce the shortcomings induced by the discrete-time approach, we conduct a half-cycle correction which is based on the assumption of uniformity within a Markov cycle [6, 32, 33]. The correction is calculated by averaging the number of individuals who are in the same state at two consecutive cycles and assigning the result to the latter cycle.

### 4.1 Force of infection

For simplicity, we exclusively account for heterosexual relationships; individuals of sex  $v$  select mating partners of the opposite sex  $v'$ . Because of the impact of the covariates, the estimation of the overall prevalence in the mating partners of sex  $v'$  is a weighted average of the prevalence in both behaviour groups of sex  $v'$ . We show the corresponding equations for the continuous-time



approach as functions of  $t$ ; for a discrete-time approach, these are similar.

The time-specific probability of selecting a partner from the high-risk group, which we indicate as  $g_{v'H}(t)$ , depends on the partner acquisition rates  $\omega_{v'H}$  and  $\omega_{v'L}$  as well as on the population sizes  $N_{v'H}(t)$  and  $N_{v'L}(t)$ . The probability of selecting a partner from the low-risk group is represented by  $g_{v'L}(t)$ . The corresponding equations adapted from [34] only account for two sexual behaviour groups and are thus extended for heterosexual mixing, to give

$$\begin{aligned} g_{v'H}(t) &= \frac{\omega_{v'H}N_{v'H}(t)}{\omega_{v'H}N_{v'H}(t) + \omega_{v'L}N_{v'L}(t)} \\ g_{v'L}(t) &= 1 - g_{v'H}(t). \end{aligned}$$

We estimate the sex-, behavioural- and time-specific force of infection

$$\rho_{v,b,1,2}(t) = \beta\omega_{vb}\bar{\psi}_{v'}(t), \quad (6)$$

where

$$\bar{\psi}_{v'}(t) = \left( g_{v'H}(t) \frac{I_{v'H}(t)}{N_{v'H}(t)} + g_{v'L}(t) \frac{I_{v'L}(t)}{N_{v'L}(t)} \right)$$

is the weighted average of the STI population prevalence, which is estimated as a function of the probabilities  $g_{v'b}(t)$  of selecting a partner of the opposite sex from one of the two sexual behaviour groups and the time-, sex- and behavioural-specific population prevalence  $\frac{I_{v'b}(t)}{N_{v'b}(t)}$ . The number of infectious individuals  $I_{v'b}(t)$  is estimated as those in the state *Infected* of the respective sex and behaviour group. In line with (4), the force of infection  $\rho_{v,b,1,2}(t)$  is a function of the STI transmission probability per partnership  $\beta$ , the partner acquisition rates  $\omega_{vb}$ , and the population prevalence  $\bar{\psi}_{v'}(t)$ .

## 4.2 Model parameters and related distributions

In addition to the probability of STI transmission  $\beta$  and the partner acquisition rates  $\omega_{vb}$ , the model contains a variety of parameters such as those determining the screening and vaccine coverage, the unit costs of STI diagnostics and treatment and the health utilities, which are relevant in context of the cost-effectiveness analysis. We specify the distributional assumptions so that both the outputs of the prevalence estimation and the health economic evaluation are within reasonable ranges.

Table 1 shows an overview of the model parameters  $\theta = \{\omega_{vb}, \chi, \beta, \pi_{r,s}, \tau, \xi, \gamma, \sigma, c, u_s\}$ . The distributional assumptions differ between the two models as follows. Since the BMM is based on a discrete-time approach, the corresponding transition probabilities are modelled using Beta distributions (constrained between 0 and 1). In contrast, the transition rates of the continuous-time BODE are modelled using Gamma distributions (defined on  $\mathbb{R}^+$ ). The transition probabilities for movements from the states *Susceptible*, *Infected* and *Asymptomatic to Dead* are assumed as identical; thus, only  $\pi_{1,5}$  is shown. The parameters of the dODE are informed by the mean values used for the BMM. Apart from the force of infection and the transition probability of remaining susceptible, we assume for simplicity that transition parameters in the three models do not differ between the sexes and behaviour groups.

To investigate the impact of probabilistic effects on the model outcome, we evaluate three scenarios including different levels of parameter uncertainty. In a *deterministic* scenario, we assume no variability in any of the parameters of the three models compared. In a scenario with *low variability*, each model parameter in the BMM and BODE is assigned a prior distribution that is tightly centered around its mean. In a scenario with *high variability*, we increase the amount of parameter uncertainty in the BMM and the BODE. This scenario is the most realistic since infectious disease modelling is commonly associated with a large amount of parameter (and possibly structural) uncertainty; this is likely to have a major impact on the economic analysis.

Table 1: Overview of the distributional assumptions for the high variability scenario. The values are fictional and were chosen so as to produce most realistic prevalence outcome and cost-effectiveness results. The mean values of the parameters are used to inform the deterministic ODE-based model.

Parameter	Description	Distribution BMM	Distribution BODE	Mean	95% estimate
$\omega_{MH}$	Partner acquisition rate (high-risk males)	Gamma(2070.25, 227.5)	equivalent to BMM	9.10	[8.70;9.50]
$\omega_{ML}$	Partner acquisition rate (low-risk males)	Gamma(8100, 4500)	equivalent to BMM	1.80	[1.76;1.84]
$\omega_{FH}$	Partner acquisition rate (high-risk females)	Gamma(1406.25, 187.5)	equivalent to BMM	7.50	[7.11;7.90]
$\omega_{FL}$	Partner acquisition rate (low-risk females)	Gamma(3025, 2750)	equivalent to BMM	1.10	[1.06;1.14]
$\chi$	Proliferation parameter	Beta(1099.99, 108899)	Gamma(1111.1,111111.1)	0.01	[0.01;0.01]
$\beta$	STI transmission probability per partnership	Beta(764.85, 4334.15)	equivalent to BMM	0.15	[0.14;0.16]
$\pi_{2,3}$	Transition parameter from state 2 to state 3	Beta(5119.2, 1279.8)	Gamma(25600,32000)	0.80	[0.79;0.81]
$\pi_{3,4}$	Transition parameter from state 3 to state 4	Beta(1842.66, 18631.34)	Gamma(2025,22500)	0.09	[0.09;0.09]
$\pi_{4,5}$	Transition parameter from state 4 to state 5	Beta(1535.96, 36863.04)	Gamma(1600,40000)	0.04	[0.04;0.04]
$\pi_{1,5}$	Transition parameter from state 1 to state 5	Beta(156.171, 312186.6)	Gamma(156.25,312500)	<0.01	[<0.01;<0.01]
$\tau$	Probability of STI diagnosis	Uniform(0.8, 1)	equivalent to BMM	0.90	[0.81;0.99]
$\xi$	Screening probability	Uniform(0.8, 1)	equivalent to BMM	0.90	[0.80;1]
$\gamma$	Vaccine coverage parameter	Beta(809.1, 89.9)	Gamma(8100,9000)	0.90	[0.88;0.92]
$\sigma$	Vaccine efficacy parameter	Beta(809.1, 89.9)	Gamma(8100,9000)	0.90	[0.88;0.92]
$c_{screen}$	Unit cost of screening in £	Lognormal(2.996, 0.693)	equivalent to BMM	25.39	[5.19;77.53]
$c_{vac}$	Unit cost of vaccination in £	Lognormal(5.011, 0.01)	equivalent to BMM	150.02	[147.14;152.98]
$c_{test}$	Unit cost of STI test in £	Lognormal(2.996, 0.03)	equivalent to BMM	20.01	[18.83;21.19]
$c_{blood}$	Unit cost of blood test in £	Lognormal(3.401, 0.03)	equivalent to BMM	30	[28.26;31.79]
$c_{treat}$	Unit cost of treatment in £	Lognormal(8.517, 0.015)	equivalent to BMM	4999.78	[4853.56;5149.24]
$c_{dis}$	Unit cost of disease treatment in £	Lognormal(9.210, 0.01)	equivalent to BMM	9999.95	[9802.97;10198.10]
$c_{gp}$	Unit cost of visit to general practitioner in £	Lognormal(3.912, 0.02)	equivalent to BMM	50.01	[48.08;52.01]
$u_2$	Health utility of infected (min=0, max=1)	Beta(1469.3, 629.7)	equivalent to BMM	0.70	[0.68;0.72]
$u_3$	Health utility of asymptomatic (min=0, max=1)	Beta(1439.4, 959.6)	equivalent to BMM	0.60	[0.58;0.62]
$u_4$	Health utility of morbid (min=0, max=1)	Beta(629.7, 1469.3)	equivalent to BMM	0.30	[0.28;0.32]

The dODE is estimated using the R packages **EpiModel** [35] and **deSolve** [36], while for the BMM and BODE, we estimate the parameters using a MCMC procedure, running 2 chains with a total of 10000 simulations and discarding the first 500. We run the simpler BMM in **JAGS** [37], while the BODE is fitted in **Stan** to deal more efficiently with the ODE system. We assess convergence using standard tools such as the Potential Scale Reduction  $\hat{R}$  and the effective sample size [29]. The relevant model codes are presented in the appendix.

In the deterministic scenario, running the dODE takes 0.22 seconds, whereas the BODE and the BMM take 0.64 seconds and 0.09 seconds, respectively. In the non-deterministic scenarios the BMM runs in 95.96 seconds, whereas the BODE runs in 188.50 seconds.

### 4.3 Prevalence estimation

We first estimate the prevalence output of the three models as follows. In the ODE-based models, we divide the overall number of infectious individuals  $I_{vb}(t)$  by the corresponding population size  $N_{vb}(t)$ , resulting in the time-specific STI prevalence. Although in the BMM time is represented by intervals, the prevalence estimation is comparable to the ODE-based models. In our case study, assumptions on discrete time in the BMM do not seem to have an impact on the results since we found the STI prevalence outcome with and without half-cycle correction to be identical in all scenarios evaluated.

In all three scenarios, we estimate STI prevalence for the overall population. Obviously, prevalence is higher in males than in females as a consequence of differences in partner acquisition rates; furthermore, due to a higher number of partners, the high-risk sexual behaviour group results in a considerably higher STI prevalence. However, the main focus of our analysis is to compare the three models rather than accounting for differences in prevalence outcomes in the subgroups of the population. Thus, we only present the overall prevalence outcomes and display them graphically for the two scenarios including parameter uncertainty.

In addition to the mean prevalence output, we show 95% confidence bands for the BMM and BODE. As for the dODE, we display the range of values at the extremes through a scenario analysis. To conduct the analysis for the 2.5% quantile, we use the lower limits of the 95% CIs of the BMM parameters as input to inform the parameters of the dODE. The scenario analysis for the 97.5% quantile is performed accordingly, using the upper limits of the 95% CIs.

Unsurprisingly, in the deterministic scenario, the outcome of the dODE, BMM and BODE is virtually identical and thus the corresponding results are not presented. Figure 2 shows the mean prevalence outcome for the scenarios incorporating a lower and higher amount of parameter uncertainty in the panels on the left and right, respectively. In the scenario with a low amount of parameter uncertainty, the mean prevalence of the three models is very similar, although the ranges of the confidence bands for the probabilistic models are slightly wider than those of the deterministic sensitivity analyses. The confidence bands for the probabilistic models are approximately identical.

In the scenario with higher variability, the differences between the dODE and the mean BMM and BODE output increase, resulting in a more conservative outcome of the BMM and BODE with a higher STI prevalence estimate. The scenario analyses of the dODE show the wider range of the parameters. In contrast to the scenario with lower variability, the bounds of the confidence bands of the BMM and BODE are lower than the extremes of the scenario analyses. The model outputs of the mean STI prevalence and the lower bound of the 95% CIs in the BMM and the BODE are approximately identical. In contrast, the upper bound of the 95% CI of the BODE is slightly wider in the beginning of the follow-up, and from year 60, the situation is reversed. Nevertheless, these differences are minor. Our results clearly show that the BMM approximates the BODE very closely.

### 4.4 Cost-effectiveness analyses

In cost-effectiveness analyses, costs generated by the interventions are compared to their induced benefits, e.g. an improvement in the quality of life. The quality of life of individuals in certain states is described by so-called utilities, typically ranging between 0 and 1, representing death and perfect health, respectively. These are used to compute the Quality-Adjusted Life Years (QALYs). We denote the unit costs and utilities as  $c_{sti}$  and  $u_s$ , with indices  $s$ ,  $t$  and  $i$  representing states  $s \in \{1, \dots, S\}$ , observation time points  $t$  and interventions  $i = 1$  (status quo) and  $i = 2$  (vaccination). We assume decreasing utility values for more severe states. Costs are induced by screening, vaccination, a visit at the general practitioner and diagnostic tests. Following a positive STI diagnosis, further diagnostic tests and treatment are necessary. For all these quantities, the distributional assumptions are presented in Table 1.

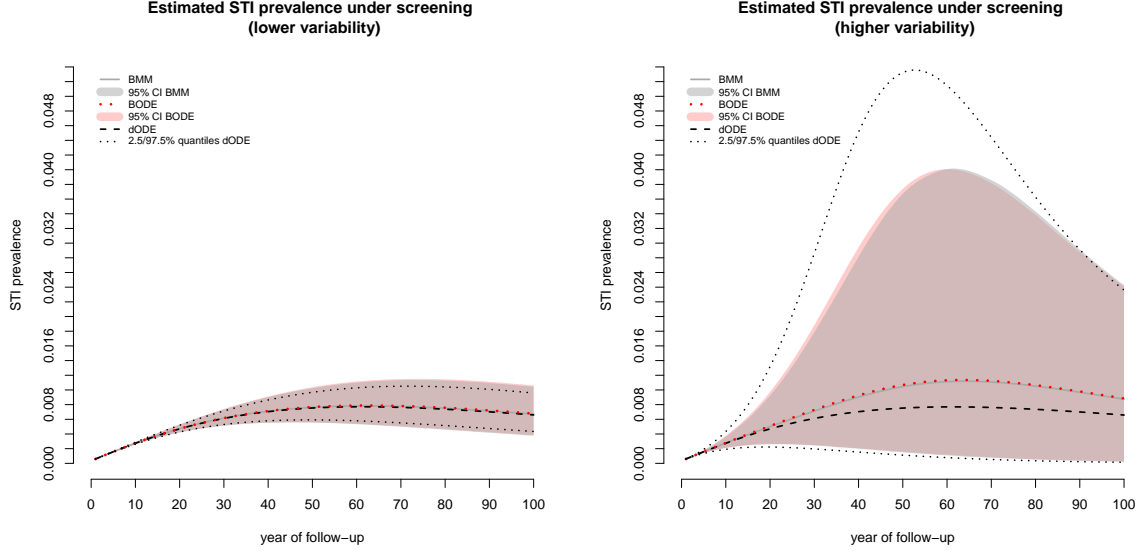


Figure 2: Deterministic ODE-based model, mean Bayesian ODE-based model and mean Bayesian Markov model output comparison of the chronic STI prevalence. The left panel shows the scenario with lower variability, whereas the scenario with higher variability is displayed on the right panel. The results of the deterministic ODE-based model are displayed by black dashed lines, whereas the mean prevalence output of the Bayesian Markov and ODE-based models are drawn by grey solid and red dotted lines, respectively. Scenario analyses of the deterministic ODE-based model are shown by black dotted lines for the 2.5% and 97.5% quantiles, respectively. Uncertainty in the probabilistic Bayesian Markov and ODE-based models is displayed by grey and red 95% confidence bands, which mainly overlay.

The overall costs per intervention are calculated as

$$C_i = \sum_{t=1}^T \sum_{s=1}^S \frac{c_{si} n_{sti}}{(1 + \delta)^{t-1}},$$

where  $n_{sti}$  are the number of individuals in state  $s$  at time  $t$  when intervention  $i$  is applied and  $\delta$  is the discount rate. In both the continuous- and discrete-time approaches, the model output on the natural history of disease infection and progression is evaluated at pre-specified time points  $t \in \{1, \dots, T\}$ , where  $T$  represents the end of follow-up. Costs and benefits induced in the distant future have a lower impact on the results since they include a higher amount of uncertainty due to unknown future events; furthermore, individuals gain most from an instant improvement of their health condition. Therefore, we discount both costs and benefits at a fixed rate  $\delta = 0.03$ , following ISPOR recommendations [38]. Similarly, the overall utilities are computed as

$$U_i = \sum_{t=1}^T \sum_{s=1}^S \frac{u_s n_{sti}}{(1 + \delta)^{t-1}}.$$

The overall costs and benefits can be re-scaled to compute the population averages

$$\mu_{ci} = \frac{C_i}{n_i} \quad \text{and} \quad \mu_{ei} = \frac{U_i}{n_i},$$

where  $n_i = \sum_t \sum_s n_{sti}$  is the total number of individuals in the virtual cohort. These can be used to define the monetary net benefit  $NB_i(\theta) = k\mu_{ei} - \mu_{ci}$ . This quantifies the utility of intervention  $i$  as a function of a parameter of *willingness to pay*  $k$ , which determines the amount of money

that the decision-maker is willing to invest to increase the benefits by one QALY. The economic evaluation is performed by calculating suitable summaries such as: the increment in mean cost  $\Delta_c = \mu_{c2} - \mu_{c1}$  and the increment in mean effectiveness  $\Delta_e = \mu_{e2} - \mu_{e1}$  between vaccination and the status-quo, or the incremental cost-effectiveness ratio

$$\text{ICER} = \frac{E[\Delta_c]}{E[\Delta_e]}.$$

In the BMM and BODE, these quantities are estimated directly as function of the parameters, while in the dODE, we conduct a scenario analysis including the 2.5% and 97.5% quantiles of the ICER to evaluate the range of “plausible” results. A cut-off point of a *willingness-to-pay*  $k$  of approximately £20 000 – £30 000 per QALY gained, adopted by NICE [39], is used as the benchmark of value for money.

As for PSA, it is usually based on: (i) the analysis of the cost-effectiveness plane, depicting the joint probability distribution of  $(\Delta_e, \Delta_c)$ ; (ii) the cost-effectiveness acceptability curve CEAC  $= \Pr(k\Delta_e - \Delta_c > 0)$ , which shows the probability that the reference intervention is cost-effective as a function of the willingness to pay  $k$ ; and (iii) the expected value of “perfect” information

$$\text{EVPI} = E_{\theta} \left[ \max_i \text{NB}_i(\theta) \right] - \max_i E_{\theta} [\text{NB}_i(\theta)],$$

which quantifies the maximum amount of money that the decision-maker should be willing to invest (*e.g.* in a new study) in order to resolve parameter uncertainty and thus make a “better” decision. The probabilistic models can perform these analyses in a straightforward way, since these quantities are all functions of the model parameters and thus a full posterior distribution can be directly obtained.

The BODE and dODE result in identical ICERs of £13 774, whereas the ICER of the BMM is slightly higher at £13 854. These differences do not have a significant impact on the decision-making process. Accounting for a higher amount of parameter uncertainty in the BMM and the BODE, the cost-effectiveness analysis results of the three models differ more widely, resulting in an ICER of £13 704 in the dODE, £7 084 in the BMM and £6 800 in the BODE. The lower ICERs in the probabilistic models are a consequence of the conservative estimate of the STI prevalence when compared to the dODE. The higher the estimated population prevalence, the lower the ICER; if an intervention such as vaccination can prevent more disease cases in a population and therefore show its full potential, it will result in a more cost-effective outcome.

For the dODE, we conduct scenario analyses to estimate the 2.5% and 97.5% quantiles of the ICER, resulting in £−13 660 and £133 620, respectively. To estimate the 2.5% quantile of the ICER, the 97.5% quantile of the prevalence outcome is used since a high prevalence results in a low ICER. This effect is reinforced by using the 97.5% quantiles of screening coverage, 2.5% quantiles of vaccine coverage, 2.5% quantiles of costs induced by vaccination, 97.5% quantiles of costs induced by screening and the STI, and 2.5% quantiles of the utilities of the states. The scenario analysis of the 2.5% quantile of the ICER is conducted accordingly; however, the assumptions on the prevalence calculation, coverage rates, costs and utilities are reversed. This scenario clearly shows the differences in the results of cost-effectiveness analyses when parameter uncertainty is ignored or accounted for. If deterministic rather than probabilistic methodology is used, the cost-effectiveness potential of certain interventions might not be recognized. As a consequence, effective and affordable interventions might be withheld from the population, resulting in a significant deterioration of overall population health.

Figure 3 displays the cost-effectiveness plane for the BMM and BODE in grey and black, respectively, showing the effectiveness-differential in QALY on the  $x$ -axis and the cost-differential in £ on the  $y$ -axis. The vast majority of points in both models lie within the sustainability area or close to its border, indicating that vaccination is cost-effective at a threshold of £25,000 when compared to screening.

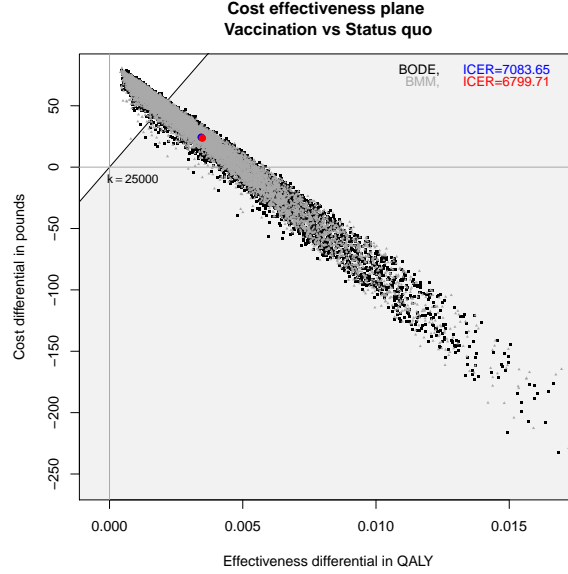


Figure 3: The cost-effectiveness plane indicates that vaccination is less expensive and more effective than the status-quo of STI screening. Most points are within the sustainability area, showing that vaccination is cost-effective. The results of the Bayesian Markov model are displayed in grey, whereas those of the Bayesian ODE-based model are shown in black. Additionally, the Incremental Cost-Effectiveness Ratios are displayed as a red and blue dot for the Bayesian Markov model and the Bayesian ODE-based model, respectively. The joint distributions of cost- and effectiveness differentials of both models are comparable.

Figure 4 shows the outputs of the CEACs and the EVI analyses. The CEACs reach values of only around 30% cost-effectiveness at the break-even points of £ 7 084 and £ 6 800, respectively, and a value of 80% is reached at a willingness-to-pay of around £ 40 000 in both models. The EVI analyses result in values of around £ 23 per individual in the BMM and BODE, which is considerably low. The results indicate that the amount of uncertainty in the BMM and the BODE is basically identical which is in accordance with the confidence bands shown in Figure 2.

## 5 Conclusions

In this paper we have presented a comparison of modelling methods for the economic evaluation of interventions in infectious disease. We acknowledge that ODE-based models have several advantages and consider the Bayesian ODE structure as ideal to combine transmission modelling with economic evaluation. However, the large computational burden associated with such strategies effectively acts as a barrier to the application of complex economic modelling in this area and possibly explains why the extensive application of PSA is limited in comparison to many other disease areas, in health economics.

Our proposal of a Bayesian dynamic Markov model can be seen as an effective compromise between the ideal fully probabilistic ODE-based models and simpler structures that fail to account for population dynamics. While providing a sparser temporal resolution in the way in which transmission is modelled, the Bayesian dynamic Markov model has the advantage of allowing a fully probabilistic analysis. This in turn means that standard economic analysis, including PSA, can be performed in a straightforward way. In addition, Markov models are a well established tool in health economics, which may facilitate the translation of the modellers' work to the regulators and assessors.

In the fictional example presented in this paper, our Bayesian dynamic Markov model per-

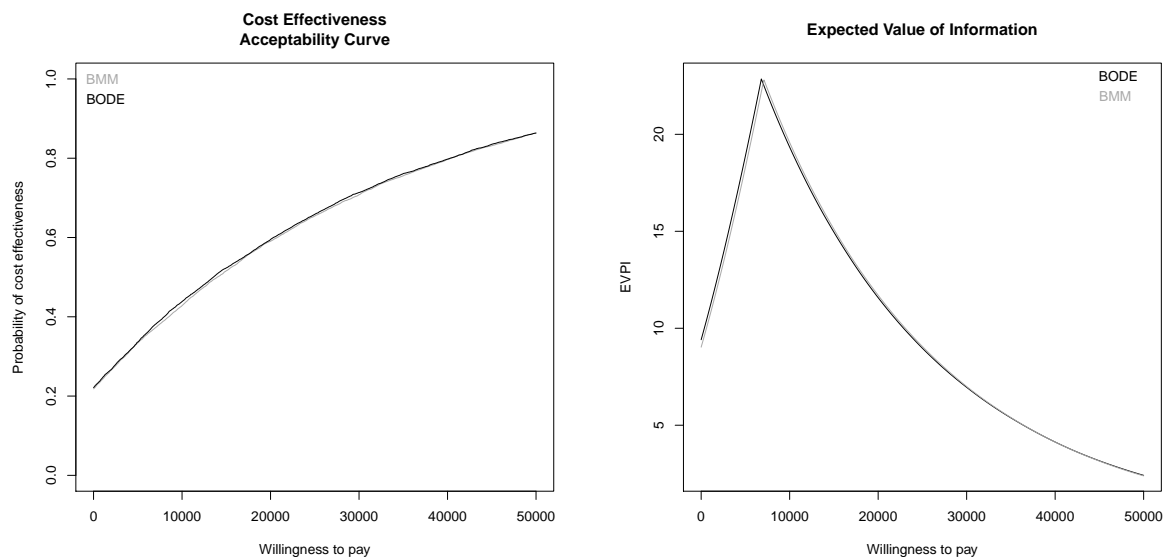


Figure 4: In line with the previous figure, the results of the Bayesian Markov model are displayed in grey, whereas those of the Bayesian ODE-based model are shown in black. The Cost-Effectiveness Acceptability Curves only reach values of around 30% at the break-even points of around £ 7 000, and 80% cost-effectiveness is attained at a willingness-to-pay of around £ 40 000 in both models. The Expected Values of Information are considerably low at around £ 23, indicating that the value for additional research is limited.

forms just as well as the BODE, with seizable computational savings. Interestingly, both probabilistic models show some difference in comparison to the base-case analysis based on a standard ODE model, when uncertainty in the underlying parameters is assumed to be substantial. This is relevant as it is often the case that the crucial elements of the transmission model are not known with high precision.

From the technical point of view, constructing a Bayesian dynamic Markov model is relatively simple and does not require the use of specialised software — in fact our analysis has been performed using **R** and **JAGS**, which are often used by statisticians and health economic modellers and thus by reviewers and advisers for health technology assessment agencies. This may again facilitate the communication of complex modelling assumptions and thus the economic assessment of complex interventions such as those based on vaccination programmes.

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